REMARKS

Claims 1 – 38 are currently pending in the application. Claims 22 – 38 are cancelled. Claims 1 – 21 are under examination in this application. Claim 1 is amended. New claim 39 is added. No new matter has been added, support being found throughout the specification and from the pending claims.

Applicants point out specifically that support for the amendment and new claim can be found in the abstract and throughout the specification. In particular, support in the specification for the amendment to claim 1 to include "wherein the fluorescence generated from the hybridization of Probe A to unwanted DNA or RNA is quenched by hybridization of probe B" can be found throughout the specification, for example at paragraph [0022].

The Examiner indicates the application contains claims 22 – 38 that are drawn to an invention nonelected with traverse in the response filed February 3, 2006. In the Amendment dated June 28, 2006, Applicant has indicated in the claims and in the Remarks that claims 22 – 38 were withdrawn from consideration.

Claim Rejections- 35 U.S.C. § 112, second paragraph

The Examiner has maintained the prior rejection of claims 1 – 21 under 35 U.S.C. § 112, second paragraph. The Examiner alleges "the claims are indefinite over the recitation 'wanted and unwanted'." The Examiner argues that the phrase "wanted and wanted" is indefinite because "the specification does not provide a complete and clear definition for the parameters that define the wanted and unwanted nucleotide sequence ((Office Action 1/05/07, p.2))." Claim terms are to be interpreted in light of the intrinsic evidence (i.e., the claims at issue, the specification, and the prosecution history. See, e.g., *McGill Inc. v. John Zink Co.*, 736 F.2d 666, 673-675, 221 U.S.P.Q. 944, 948-951 (Fed. Cir. 1984), cert. denied, 105 S.Ct. 514 (1984); *Fromson v. Advance Offset Plate, Inc.*, 720 F.2d 1565, 1569-1571, 219 U.S.P.Q. 1137, 1140-1141 (Fed. Cir. 1983)). Moreover, claims should be construed as they would be by those skilled in the art. *Fromson,* 720 F.2d at 1571, 219 U.S.P.Q. at 1142. That is, the "text and procedure" to be consulted is the application itself. The recitation 'wanted and unwanted' is therefore not indefinite because the specification provides examples of such conditions, and, moreover, the art itself recognizes these terms. Nowhere does 35

U.S.C. § 112, second paragraph require that the Applicant provide "a clear, complete and fixed" definition for 'wanted and unwanted', as alleged by the Examiner in paragraph 2 of the Office Action of 1/05/07, p.2.

The terms 'wanted and unwanted' are described completely such that one of skill in the art would be able to make and use the invention. For example, the specification provides description in a number of different passages of what is meant by "wanted and unwanted" nucleic acid sequences. See, for example, paragraphs [0020], [0026], [0027], [0031], [0097], and also Example 1.

The specification teaches that:

> (a)s an important aspect of the invention, the quencher-labeled probe hybridizes to the unwanted target but not to the wanted target hereby eliminating unwanted signal without interfering with the fluorescent signal generated from the binding of the fluorescent-labeled probe to the wanted target [0026].

The specification teaches one of skill in the art the difference between what a wanted and unwanted nucleotide sequence would be, and defines the parameters of a wanted and unwanted nucleotide sequence in terms of the probes that bind to them. The specification teaches one skilled in the art (1) what the properties of the probes that bind to wanted and unwanted are (see, for example, paragraph [0020]), (2) how the target sequences are defined by their binding to the specificity to the probes (see, for example, paragraph [0027]), and provides a working example in Figure 1A or hybridization of probes to wanted and unwanted target sequence (see, for example, paragraph [0031]). Further, Example 1 teaches pairs of PNA probes suitable for the analysis of *Staphylococcus aureus* optionally present in a sample where unwanted hybridization of the labeled probe to *Staphylococcus schleiferi* rRNA is quenched by hybridization of a quencher-labeled probe hybridizing to *Staphylococcus schleiferi* rRNA, but not to *Staphylococcus aureus* rRNA. Thus, the specification clearly teaches one of skill in the art exemplary difference between wanted and unwanted nucleotide sequences.

Moreover, Applicants note that the Examiner cites the Heller (US 5,532,129; the '129 patent) and Elsas et al (US 6,207,387; the '387 patent) references, and argues on page 5 of the 10/13/2006 Office Action that the '129 and '387 patents "teach a method requiring the use of two probes, wherein one probe is complementary to a *wanted* nucleic acid sequence and the second probe is complementary to an *unwanted* nucleic acid sequence..." The Examiner continues to argue

in the 1/05/2007 response that "the terms 'wanted' and 'unwanted' were used within the rejection of the claims only to point out how the methods of Heller and Elsas rendered obvious the presently claimed method (Office Action 1/05/07, p.2)." If the terms are rendered obvious by the prior art, then it is impossible for the terms to be indefinite to one of skill in the art. The art clearly recognizes what "wanted and unwanted" nucleic acid sequences are as used in hybridization methods. Applicants have clearly taught what is meant my "wanted and unwanted" nucleic acid sequences in the specification itself in order for the terms to be interpreted in view of the cited art.

The Examiner further alleges "the claims are indefinite over the recitation 'closest'." The claims have been amended to obviate this rejection.

Accordingly, Applicants respectfully request the withdrawal of the rejections and allowance of the claims.

Claim Rejections- 35 U.S.C. § 103(a)

Claims 1, 12, 13, and 21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Heller (US 5,532,129; the '129 patent), in view of Elsas et al (US 6,207,387; the '387 patent). Applicants respectfully traverse the rejection.

Claim 1 has been amended to recite the step that, "the fluorescence generated from the hybridization of Probe A to unwanted DNA or RNA is quenched by hybridization of Probe B."

The Examiner alleges that the '129 Patent teaches "a method to detect target sequences that comprises step a) hybridizing two probes, wherein one probe has a fluorophore (Probe A) and another probe that has a quencher (Probe B) ...and method step b) the subsequent detection of Probe A's flourescence as an indication of the presence of a target sequence (page 5, Office Action, May 1 2006)." The Examiner admits, however, that the '129 patent does not teach a method wherein the probes have wanted and unwanted sequences. The Examiner argues that the '387 patent cures the flaws of the '129 patent and teaches "of anchor and detection probes that detect mutations (page 6, Office Action May 1, 2006)." The Examiner further alleges that Probe A of the '129 patent is the detection probe because it has wanted and unwanted sequences, and Probe B is

represented by the anchor probe. The Examiner argues that it would have been prima facie obvious to modify the teachings of the '129 patent with the improvement of designing probes with wanted and unwanted sequences as taught by the '387 patent.

Neither the '129 patent nor the '387 patent, alone or in combination, teach or suggests a method wherein the fluorescence generated from the hybridization of Probe A to unwanted DNA or RNA is quenched by hybridization of Probe B. The instant claims teach a method which increases the specificity of an assay by preventing signal evolution from the unwanted target.

The '387 patent does not cure the flaws of the '129 patent. The '129 patent, as the Examiner points out, "teach a method requiring the use of two probes, wherein one probe is complementary to a wanted nucleic acid sequence and the second probe is complementary to an unwanted nucleic acid sequence and wherein the fluorescence emitted from the probe complementary to the wanted nucleic acid sequence is detected as indicative of the presence of the wanted nucleic acid in a sample." The '129 patent neither contemplates nor suggests use of the probe complementary to the unwanted sequence in a method to decrease signal evolution from the unwanted target. The '387 patent does not cure this flaw. The '387 patent merely teaches that "when the allele specific probe and the anchor are hybridized the fluorescence is quenched." Together, it would not have been obvious to modify the teachings of the '129 patent with the teachings of the '387 patent to teach or suggest a method according to the instant claims.

Applicants respectfully request withdrawal of the rejection and allowance of the claims.

Claim 14 stands rejected under 35 U.S.C. 103(a) as being unpatentable over the '129 patent in view of the '387 patent and in further view of Meade et al (US PGPUB 2001/0046679). Applicants respectfully traverse the rejection.

The combination of the '129 and '387 references do not make the subject matter of the instant claims obvious for the reasons stated above. The US PGPUB 2001/0046679 document, like the teaching of the '129 patent, merely provides systems and schemes for probe design, but does not teach or suggest "wherein the presence or amount of wanted DNA or RNA present in the sample can be positively correlated with the fluorescence of the fluorophore of Probe A."

Applicants respectfully request withdrawal of the rejection and allowance of the claims.

Claims 2 – 11 and 15 – 20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over the '129 patent in view of the '387 patent et al and in further view of Oliveira et al (Journal of Clinical Microbiology, 2002, Vol. 40, N0. 1, pages 247-251) in view of GenBank S83568 and in further view of Hogan et al (WO0066788). Applicants respectfully traverse the rejection.

The combination of the '129 and '387 references do not make the subject matter of the instant claims obvious for the reasons stated above. Thus, a combination of the '129 patent, the '387 patent and Oliveria does not render the rejected claims obvious. The combination of references fails to teach or suggest, "wherein the presence or amount of wanted DNA or RNA present in the sample can be positively correlated with the fluorescence of the fluorophore of Probe A." The methods of Oliveira are different from those claimed in the instant invention. Further, the methods of Oliviera teach away from the instant invention, showing weak cross-hybridization of the *Staphylococcus aureus* specific probe with *Staphylococcus schleiferi*. Further, Oliveira points out that a *S. aureus* specific probe to this particular region of 16S ribosomal RNA was originally described in a 1993 article (Bentley et. al. Lett. Appl. Microbiol. 16:203-206), and the same probe region was used again in 2000 for FISH experiments (Kempf et. al. J. Clin. Microbiol. 33:50-52). This probe sequence is specific, but it does create false positive results with *S. schleiferi* despite its nature as PNA probe and use of design rules by Hogan. Those skilled in the art, including Oliveira, were unable to generate a high affinity PNA probe (for FISH), despite their efforts, and in addition to the aid of many years of precedent, and the state of the existing technology.

Applicants request withdrawal of the rejection and allowance of the claims.

In view of the above amendment, Applicants believe the pending application is in condition for allowance.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 58576(48497).

Dated: January 12, 2007

Respectfully submitted,

By _____
Jonathan M. Sparks, Ph.D.
Registration No.: 53,624
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 439-4444
Attorneys/Agents For Applicant